Hepatic Angiosarcoma in a Child: Successful Therapy With Surgery and Adjuvant Chemotherapy

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We report a 3-year and 11-month-old Caucasian female, who initially presented with an unresectable hepatic angiosarcoma. After three courses of chemotherapy with adriamycin/cisplatin, the tumor decreased in size considerably, allowing complete surgical resection. She also received postoperative chemotherapy with alternating cycles of ifosfamide/etoposide, cisplatinum/adriamycin, and vincristine/actinomycin D/cyclophosphamide for 18 months. She remains disease-free for greater than 44 months from the initial diagnosis. Our experience suggests that total excision of the tumor, together with an aggressive chemotherapy regimen, can improve the disease-free survival for children with this highly malignant vascular tumor of the liver. **Med. Pediatr. Oncol. 28:139–143**
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Key words: hepatic tumors; angiosarcoma; chemotherapy; complete surgical excision

INTRODUCTION

Angiosarcoma of the liver is a rare malignancy with fewer than 30 pediatric cases reported in the English literature [1–10]. This is a highly malignant vascular tumor of endothelial cell origin [11], and has a grave prognosis.

Previously published literature on pediatric hepatic angiosarcoma has suggested that surgical resection alone or in combination with multi-agent chemotherapy with or without radiotherapy rarely provides a long-term disease-free survival [1,3–5,8,9]. We report a patient with hepatic angiosarcoma, who underwent complete surgical resection with pre- and postoperative adjuvant multi-agent chemotherapy. She remains free of disease for greater than 44 months from the initial diagnosis.

PATIENTS AND METHODS

A 3-year and 11-month-old Caucasian female presented in January of 1992 with a 3-day history of fever, rhinorrhea and decreased appetite. She also gave a history of having a "mass"-like feeling in her abdomen. On physical examination, a hard, nodular mass was noted in the right upper quadrant. An abdominal ultrasound showed a large, solid homogenous mass that arose from the right lobe of the liver. She was referred to Texas Children's Hospital for further evaluation. Her past medical history did not reveal any prior history of jaundice or liver disease.

On physical examination, her abdomen appeared protuberant and a large, hard mass with a nodular surface was palpated in the right upper quadrant, extending to 10 cm below the right costal margin. There was no splenomegaly. There was no evidence of jaundice. Her cardiovascular function was normal and the remainder of the physical examination was unremarkable. The initial laboratory tests revealed a hemoglobin of 11.9 g/dl (normal 12–13 g/dl); platelet count of 294,000/mm^3 (normal 150,000–450,000/mm^3); white cell count of 13.1×10^3/mm^3 (normal $5–15 \times 10^3$/mm^3) with a normal differential count. Liver function tests showed ALT 39 IU/L (normal 10–25 IU/L); AST 21 IU/L (normal 15–50 IU/L); LDH 1253 IU/L (normal 470–900 IU/L); alkaline phosphatase 188 IU/L (normal 150–380 IU/L); serum bilirubin-indirect 0.5 mg/dl (normal 0.0–0.9) and direct bilirubin <0.1 mg/dl (normal 0.0–0.34 mg/dl). Renal function tests revealed a BUN of 8 mg/dl (normal 5–25 mg/dl) and serum creatinine of 0.4 mg/dl (normal 0.2–1.2 mg/dl). Serum alpha fetoprotein level was 2.2 ng/ml. A computerized tomography (CT) scan of the abdomen and pelvis (with and without contrast) demonstrated a large, inhomogenous soft tissue mass arising from the liver (Fig. 1A). The mass appeared to arise from the anterior segment of the right lobe of the liver, but extended into the posterior segment of the right lobe and medial segment of the left lobe. A probable tumor nest was also noted near the falciform ligament. There was no evidence of abdominal or retroperitoneal adenopathy or other evidence of metastases. Chest CT scan and bone scan were normal. Bone marrow aspirate and biopsy showed no evidence of infiltrative disease.

The patient underwent exploratory laparotomy, and

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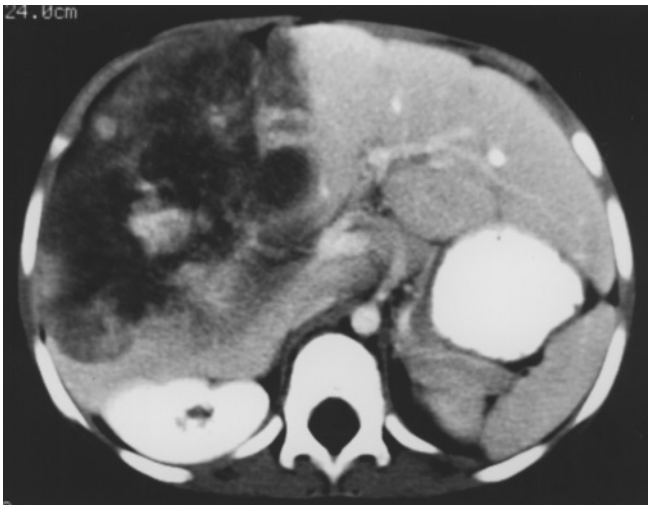

Fig. 1. **A:** CT scan at diagnosis demonstrates a heterogeneous, partially enhancing mass involving the right lobe of the liver with extension into the medial segment of the left lobe. **B:** CT scan at optimal chemotherapeutic response shows marked reduction of tumor with involvement confined to the right lobe.

biopsy of the abdominal mass (right hepatic lobe and medial segment of the left lobe of the liver) was performed. The tissue was soft and pink-tan in gross appearance. On microscopic examination, there was extensive replacement of the liver architecture by a poorly differentiated neoplasm which was sometimes separated by irregular bands of fibrosis and infiltrated the parenchyma diffusely, replacing hepatocytes but sparing bile ducts and ductules (Fig. 2). Tumor cells were pleomorphic with large nuclei and a moderate amount of pink cytoplasm. Numerous mitoses including abnormal ones were noted. Acellular globules that stained pink with Hematoxylin-eosin (H&E) stain were scattered throughout. These also

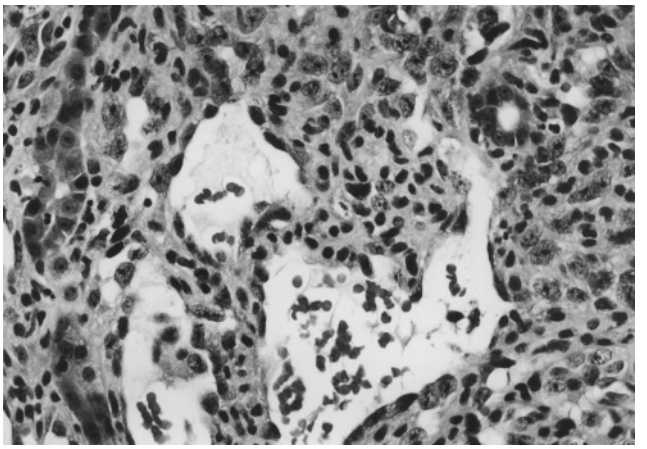

Fig. 2. Liver biospy. A representative area of the biopsy shows a few residual bile ducts separated by a mixture of irregular channels with relatively flat endothelial cells interspersed with plump undifferentiated cells that are dividing actively and have prominent nucleoli in vesicular nuclei. (Hematoxylin-eosin $\times$ 400.)

stained with α-1 antitrypsin, Periodic acid-Schiff (PAS) and factor VIII. Small dilated channels lined by plump cells were also noted in several areas. These cells were decorated by the anti-CD34 antibody (QBEND/10) (Serotec, Oxford, UK) (serotec). The final pathologic diagnosis was poorly differentiated angiosarcoma of the liver.

The patient received three courses of chemotherapy with cisplatinum/adriamycin, every 3–4 weeks. She was reevaluated at that point with a CT scan of the abdomen and pelvis. This indicated that the tumor had decreased in size by 70% (Fig. 1A and B). The abnormality earlier seen in the left lobe was no longer identified. Chest CT scan was normal. She was considered to be in partial remission at this time, and underwent an abdominal surgical reexploration. A right hepatic lobectomy with complete resection of the tumor as well as a biopsy of the previous tumor site in the medial segment of the left lobe was done in early April 1992. Although most of the tumor was necrotic, substantial foci of actively dividing neoplastic cells remained. There was a higher percentage of vascular channels than in the pretreatment biopsy but nests of malignant cells were still present.

The patient received postoperative chemotherapy for 18 months with alternating cycles of ifosfamide/etoposide and cisplatinum/adriamycin. After three postoperative cycles, when her cumulative adriamycin dose was 450 mg/M^2, her chemotherapy regimen was changed to alternating courses of ifosfamide/etoposide and vincristine/actinomycin D/cyclophosphamide (Fig. 3). No radiotherapy was administered.

She completed chemotherapy with no evidence of cardiac toxicity. She has evidence of renal tubular dysfunction due to ifosfamide and requires electrolyte supplementation. The patient developed severe sensorineural hearing

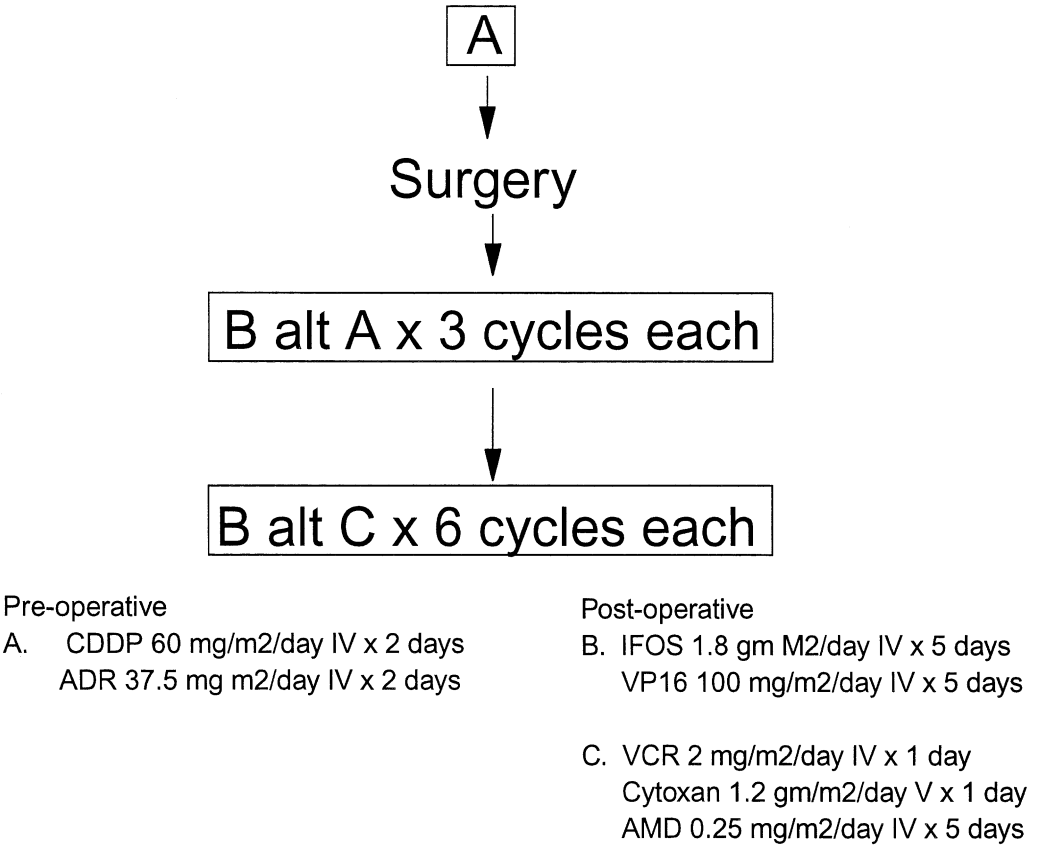

Fig. 3. Chemotherapy regimen.

loss secondary to cisplatinum, and requires amplification. She is currently excelling in the second grade.

DISCUSSION

Angiosarcoma of the liver is an unusual malignant neoplasm in the pediatric population [4]. It is a rare hepatic tumor that occurs almost exclusively in adults with a peak incidence in the sixth and seventh decades of life [15]. A small number of pediatric cases have been reported. The age at presentation ranges from 2 months to 15 years, with a mean age of 3.9 years [5,9]. Childhood hepatic angiosarcomas occur predominantly in females, with a female:male ratio of about 2:1 [5,9]. In adults, this neoplasm has been associated with etiologic factors such as thorotrast (thorium dioxide), vinyl chloride, arsenic, androgenic anabolic steroids and oral contraceptives [12–14]. These factors are usually not associated with the childhood disease, but one patient with childhood hepatic angiosarcoma associated with elevated environmental arsenic exposure has been described in the literature [8]. Selby et al. [9] have described two patients who appear to have angiosarcomas arising in infantile hemangioendotheliomas. Two other patients with type I hemangioendotheliomas in infancy have developed malignant angiosarcomas 4–5 years after initial presentation [4,6,7]. Falk et al. [8] described four cases of fatal hepatic angiosarcoma in children following biopsy diagnoses of benign hemangioendothelioma or hepatoblastoma.

Patients usually present with an abdominal mass associated with other symptoms and signs such as jaundice, abdominal pain or fatigue [5,15]. Vomiting, fever, tachypnea, pallor, high output congestive cardiac failure or hemorrhagic ascites may also be associated features [9]. Kasabach-Merritt syndrome, intraperitoneal bleeding [16] and disseminated intravascular coagulation [15] have been described in adult patients with hepatic angiosarcomas but are rare in children. Angiosarcoma metastasizes to lungs, bone, lymph nodes, adrenal glands and kidneys [5,9].

Information regarding management and prognosis of childhood hepatic angiosarcoma is not readily available due to the rarity of this tumor. Treatment strategies including multi-agent chemotherapy, surgical resection and radiotherapy have rarely increased the reported survival for children with hepatic angiosarcoma [5,9]. Multi-agent chemotherapy following initial complete surgical resec-

tion has been reported to be successful in some cases of hepatic angiosarcomas. The regimens contain chemotherapy agents known to be effective against pediatric sarcomas. Selby e al. [9] reported a series of 10 cases. In this review, three patients underwent complete resection of the tumor, followed by radiotherapy (XRT), chemotherapy (unspecified) or chemotherapy with etoposide/adriamycin/cisplatinum with hepatic artery embolization, respectively. Two patients had biopsy only, followed by chemotherapy. Treatment data for the remaining five patients is unknown. Only one patient following initial complete resection and unspecified chemotherapy was alive and disease-free at 32 months of follow-up. Kirchner et al. [6] described a 4-year-old patient who was treated with complete resection initially followed by XRT and adjuvant chemotherapy with 5-fluorouracil, vincristine and adriamycin. She remained disease-free 24 months from diagnosis at the time of report.

Chemotherapy used in our patient's pre- and postoperative regimen was selected based on current soft tissue sarcoma treatment regimens. Combination therapy with cisplatin and adriamycin has shown good activity against a variety of sarcomas according to published literature. Harris et al. [17] described a 7-year-old patient with a primary sarcoma of the liver which was nonresectable initially, but was completely resected following chemotherapy with cisplatin and adriamycin. Our patient was similar in that preoperative chemotherapy with adriamycin/cisplatin decreased the tumor size significantly, allowing complete resection of the tumor. Therefore, it appears that hepatic angiosarcoma may show a good response to combination chemotherapy with adriamycin and cisplatinum used in this manner. Adriamycin may be the active agent in this drug combination. Adriamycin given in combination with cyclophosphamide and methotrexate has been effective in causing decrease in tumor size in a small series of adult patients with vinyl chloride associated hepatic angiosarcoma [18]. The dose of cyclophosphamide used in these patients was 600 mg/M^2. Our patient received cyclophosphamide 1.2 g/M^2/dose during the course of her therapy. The increased dose intensity of this agent may have contributed to the improved outcome in our patient.

The combination of ifosfamide and etoposide with the effective uroprotector mesna has been shown to be highly active in the treatment of pediatric sarcomas [19,20] and plays an important part in current pediatric sarcoma therapy. Recent literature on renal tubular dysfunction in association with ifosfamide therapy has suggested that the risk of developing renal complications is highest when the patient is <3 years of age, when a preexisting renal abnormality is present, and when more than 72 g/M^2 total dose of ifosfamide is given [21]. Our patient, who was 3 years and 11 months at the time of diagnosis, did not have a preexisting renal abnormality. She received a total dose of ifosfamide 72 g/M^2 and also had prior therapy with cisplatinum. We speculate that this drug combination may have increased her risk of developing renal tubular disease.

CONCLUSIONS

The rarity of angiosarcomas in children has precluded the development of an effective chemotherapy regimen. However, our experience suggests that an aggressive chemotherapeutic regimen and total excision of the tumor can improve the disease-free survival for children with hepatic angiosarcoma.

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